Ns 12-502

HIPPOCAMPAL STATES AND FUNCTIONAL RELATIONS WITH CORTICOSUBCORTICAL SYSTEMS IN ATTENTION AND LEARNING.

W. R. Adey

Departments of Anatomy and Physiology, and Brain Research Institute, University of California, Los Angeles.

If accepted, please send proofs to:

Dr. W. Ross Adey
Department of Anatomy
School of Medicine
University of California
Los Angeles, California, 90024

The role of the hippocampus in mechanisms of attention and learning has slowly unfolded in recent years. Evidence has accrued that it is intrinsically concerned in both acquisition and subsequent ability to perform learned habits requiring discriminative functions of a high order, as suggested by Pribram and Mishkin (1955). At the same time, however, it has become apparent that the hippocampus does not function in these mechanisms independently of subcortical zones, with which it is profoundly interconnected, nor does it appear to be the repository of memory traces in the sense of a bank or store of such engrams. Through its connections with the diencephalon and more caudal brainstem, it appears to influence, and to be influenced by, activity in sensory systems; and to be responsible for the establishment in these extrahippocampal structures of the physiological "set" that is requisite for storage of information therein. It is a challenging notion that these systems may transact information without the ability to effect its storage in the absence of appropriate interrelations with the hippocampal system.

The classical trinity of ablation, stimulation and electrophysiological recording have each played a part in the still incomplete picture of hippocampal function. During behavioral training we have noted increased regularity of pattern in both hippocampal and mesencephalic EEG records with attainment of high performance levels in visual discriminative tasks (Adey, Walter and Hendrix, 1961; Adey and Walter, 1963), and have seen a variety of complex patterns of conditional firing appear in rostral midbrain and thalamic units during classical conditioning and extinction (Kamikawa, McIlwain and Adey, 1964).

In further studies of the role of the hippocampus in learning, we have examined both intimate aspects of its intrinsic electrical activity (Porter, Adey and Brown, 1964), and simultaneous relations with other brain structures. We have also sought evidence by the use of impedance measurements for changing tissue states in the hippocampus, as well as in the amygdala and midbrain reticular formation, in the course of behavioral training with separate alerting, orienting and discriminative stimuli. We have sought differential regional responses relating to these stimuli at different levels of training and in cue reversals with retraining. The findings have further supported the view that impedance changes so evoked relate to the process of information storage in the tissue, rather than to nonspecific aspects of total tissue activity, as suggested by Jasper (1965). The relationship of impedance responses to normal neuronal content of the tissue, and differential effects of modifications in ionic environments will also be discussed.

1. Regional aspects of intrahippocampal electrical activity; effects of small electrolytic lesions.

Electrical activity in hippocampal tissue of such mammals as rat (Bremner, 1964). rabbit (Jung and Kornmüller, 1938) and cat (Adey, Dunlop and Hendrix, 1960; Grastyan, 1959) during attentive behavior has been characterized by regular wave trains at 4 to 7 cycles per second ("theta" activity). Recent studies have emphasized, however, that even in the cat, sharp regional differences exist within the hippocampus in the distribution of theta activity as a concomitant of alerted behavior, and in orienting and discriminative responses (Porter, Adey and Brown, 1964; Radulovački and Adey, 1965).

Our studies of bipolar records from transverse arrays of chronically implanted electrodes in the cat's dorsal hippocampus clearly indicated that the mere aspect of an alerted state, without either gross orienting behavior, or the imposition of a discriminative performance, was uniformly accompanied by a rich gamut of hippocampal slow waves. These waves were present particularly in leads primarily located in the dendritic zone of the pyramidal cell layer from the first moments of exposure to the test situation. By contrast, deeper regions of the dentate fascia and the subiculum typically exhibited "fast desynchronized" activity in intertrial epochs at the same time as hippocampal dendritic zones showed a spectrum of high amplitude theta waves. Nevertheless, leads exhibiting much fast activity during intertrial epochs showed a typical 6 cycles per second theta burst during discrimination, and also frequently a 4 to 5 cycles per second train during orientation (Fig. 1).

The possibility of relating such hippocampal EEG activity to finer shades of behavioral responsiveness will be discussed further below, but it may be pointed out that much continuous theta activity occurred in leads in hippocampal dendritic zones from the earliest exposure to the test situation, as a correlate of the alerted state. Our findings do not support the view that the waves in these regions arise secondarily to the development of an orienting reflex, following an initial period in which responses to unfamiliar stimuli are characterized by desynchronization and disappearance of slow waves (Grastyan, 1959). A possible solution to these seemingly incompatible findings may lie in evaluation of regional distribution of theta wave trains, by taking more critical account than has been customary of exact recording sites within the hippocampus.

Since there is considerable evidence that extensive hippocampal lesions interfere with learning and learned performance in animals and man (Adey, 1961; Barbizet, 1963; Drachman and Ommaya, 1964), we have examined the effects of a lesion in one part of the hippocampus on electrical activity in other parts of the structure, and sought changes in learned performances after small bilateral hippocampal electrolytic lesions (Porter, Adey and Brown, 1964). To this end, an array of six parallel electrodes 1 mm apart was implanted in the hippocampal arch on each side in the cat. This permitted destruction of the hippocampal arch by electrolysis through one pair of electrodes, leaving the remainder undisturbed for continuing registration of electrical activity. Behavioral training was in a modified T-maze with approach to a concealed food reward on the basis of a visual cue (light-dark discrimination). Computed averages of hippocampal electrical activity during behavioral performance were prepared from 40 daily trials. Lesions varied in size from less than 1.0 cmm to zones extending 4 to 5 mm across the hippocampal arch and a similar distance along the structure, but even the largest lesions were essentially confined within hippocampal structures.

Passage of electrolytic current was accompanied by local seizures and often also in the contralateral hippocampus. Seizure discharge usually continued for a few minutes after cessation of current flow and was followed by reduction of EEG amplitude in all leads. Recovery of amplitude occurred after 24 hours in the contralateral hippocampus, and in the ipsilateral undamaged regions (Fig. 2). High frequency components in undamaged regions recovered more slowly from the adjacent injury than the amplitude of the slow waves. Recovery of high frequency components began 3 days after the lesion was complete after about 1 week.

Computed averages of electrical activity accompanying the discriminative performance reflected the effects of the lesion. Within the lesion, there was no synchronous slow wave activity, and only slight increments in amplitude occurred thereafter. In partly damaged regions, recovery of high frequency components was also detectable a few days after the lesion. In 4 of 7 animals, computed averages from surrounding undamaged areas showed increased amplitude, apparently arising in increased synchrony of slow wave activity, and persisting for several days after the lesion (Fig. 3). This increased synchrony in the average did not appear to relate to transient loss of high frequency components noted above. Amplitude, latency and duration of synchronous 6 cycles per second activity in the averaged records, and the variability of these daily averages during constant behavioral test conditions, were not markedly changed by the electrolytic lesions.

Bilateral small lesions did not in any way alter the correct discriminative performance, even when tested only 10 minutes after the lesion, and while electrical activity was generally reduced and some abnormal spikes occurred. If the lesion produced continuing seizure activity, performance was affected during the period of electrical abnormality. Cue reversal and retraining were also tested before and after lesions. In only one of 7 cats was there a significant increase in the number of trials to reach a 90 per cent criterion after bilateral dorsal hippocampal lesions. In this animal, cue reversal was deliberately withheld before lesions were made. Another animal showed increased numbers of trials to "unlearn" the discrimination after the lesions, and a slight increase in the number of trials to reach criterion in retraining. In summary, there was little effect of limited bilateral hippocampal lesions on retention of a learned habit, or ability to acquire a new habit.

These findings are in striking contrast to the severe but temporary changes in hippocampal EEG and performance capability following subthalamic lesions, but not lesions of similar size in overlying thalamic tissue (Adey, Walter and Lindsley, 1962). Hippocampal theta trains at 6 cycles per second were absent or grossly modified during the period of impaired performance. Absence of normal theta activity following such diencephalic lesions emphasizes the significance of such hippocampo-diencephalic and -mesencephalic connections, both in relation to performance capability and in the genesis of the hippocampal theta activity as a correlate of behavioral performance. Normal patterns of theta activity thus appear to depend not only on integrity of the septum (Green and Arduini, 1954) but also on these more caudal zones of the subthalamus.

2. Effects of psychotomimetic and hallucinogenic agents on the hippocampal system.

Previous studies have indicated the hippocampal system as a prime site of action for psychotomimetic cyclohexamines (Adey and Dunlop, 1960; Monroe and Heath, 1961) and hallucinogenic amides (LSD-25, psilocin and psilocybin), with decrements in performance associated with propagation of drug-induced seizure discharges into subcortical and sensory cortical systems (Adey, Bell and Dennis, 1962).

More recent studies have shown that effects of LSD (75μ g/kg) in single doses, at intervals of not less than 3 weeks, persist for many days after the drug, at times when all aspects of seizure discharge have subsided, and baseline EEG appears identical with predrug records. Computed averages of rhythmic 6 cycles per second hippocampal and entorhinal wave trains during approach performance showed increased amplitude and regularity, maximal about 4 days after LSD, and decaying to control levels after 5 to 7 days (Fig. 4) (Adey, Porter, Walter and Brown, 1965). Midbrain reticular activity showed only minor changes over the same period.

It was noted that single doses of these drugs were followed by a substantial disinhibition of inhibited orienting behavior in the test situation. Orienting behavior present during initial exposures in the test situation, and inhibited in the course of training, was dramatically reestablished following single doses of LSD. An attempt was therefore made to study aspects of hippocampal activity that might accompany orienting behavior, and to test effects of LSD and cyclohexamines on EEG activity during orientation.

3. Comparison of EEG patterns in orienting and discriminative behavior.

The uniqueness of the orienting reflex rests on certain "principles" in the intimate behavior of its component reflexes, including their non-specificity with respect to both quality and intensity of the stimulus, and the selectivity of extinction of various properties of the stimulus with repeated presentation (Sokolov, 1963; Vinagradova, 1961).

A specific relationship between hippocampal theta wave trains and orienting behavior has been postulated (Grastyan, 1959; Grastyan, et al., 1959). However, the exquisite plasticity of hippocampal theta rhythms in changing behavioral states, including the appearance of bursts of waves in a narrow spectral range during performance of a visual discriminative task, have suggested more subtle and specific relations to discriminative functions and judgment capability (Adey, 1965; Adey, Dunlop and Hendrix, 1960; Adey, Bell and Dennis, 1962; Adey, Walter and Lindsley, 1962).

Radulovački and Adey (1965) distinguished three basic states in hippocampal EEG activity in the cat; in alert but non-performing animals, in the course of discriminative performance, and during orienting behavior. Alert but nonperforming animals exhibited a wide spectrum of "theta" waves in the range 3 to 7 cycles per second on first introduction into the test situation, without overt aspects of orienting behavior. This activity persisted in EEG epochs between discriminative and orienting trials throughout many months of training. During T-box discriminative performance, theta waves regularized at 6 cycles per second, as described above. Computed averages in orienting trials, given in the same number on each test day and randomly interspersed with the discriminative trials, showed slower and less regular averages at 4 to 5 cycles per second (Fig. 5).

Single doses of LSD-25 were followed by prolonged disinhibition of inhibited orienting behavior, and by the gradual appearance of a regular EEG average during orientations 5 to 10 days after the drug, and declining after 15 to 20 days, concurrently with the decline of orienting behavior. Similar but accelerated changes in EEG and behavior were induced by a psychotomimetic cyclohexamine, CL-400. It is concluded that hippocampal EEG patterns sensitively reflect a repertoire of behavioral responses, rather than exhibiting non-specificity as an accompaniment of a wide repertoire of specific reflexes.

The sensitivity of neuroelectric processes in the hippocampus to subtle shifts in cerebral states, and indications that hippocampal theta activity during discrimination has the characteristics of a "pacemaker," with fragmentary and less regular rhythms in midbrain reticular formation, subthalamus and primary sensory cortical areas, have suggested that deposition of a "memory trace" in extrahippocampal systems may depend on such wave trains; and subsequent recall, on the stochastic reestablishment of similar wave patterns (Adey and Walter, 1963).

In continuing studies (Elazar and Adey), specification of interrelations between the hippocampal EEG and activity in the subthalamus, midbrain reticular formation and visual cortex is being undertaken by comprehensive spectral analysis (Walter and Adey, 1965 a and b). High levels of coherence occur between hippocampal and subcortical leads, as well as with cortical leads, during discrimination. These high coherences may occur at frequencies higher than the theta range, at frequencies between 12 and 20 cycles per second. Analyses during orienting behavior have also produced widespread coherent relationships but differing in distribution from those during discrimination. Differences in coherence levels have also been detected between correct and incorrect decisions.

4. Hippocampal impedance measurements during acquisition of a learned discriminative habit.

Disclosure of patterns in cerebral slow waves consistently related to the performance of discriminative tasks suggested the possible importance of monitoring concurrent changes in functional state in the cerebral tissue generating these waves. We have used impedance measurements in restricted volumes of tissue in hippocampus, septum, amygdala and reticular formation to provide a series of correlates with states of tissue excitability, and have sought changes relating to acquisition of learned behavior (Adey, Kado and Didio, 1962; Adey, Kado, Didio and Schindler, 1963). The latter may not manifest themselves as clearly in aspects of ongoing electrophysiological activity presumably involved in transactional mechanisms, as in other more subtle measures capable of revealing changes in tissue states relating to the storage of information. In particular, there is the possibility that these storage mechanisms may not lie exclusively within the neuronal compartment, but that enveloping neuroglia may also be involved.

With microvolt signals at 1000 cycles per second applied through chronically implanted coaxial electrodes in volumes of cerebral tissue about 1.0 cmm, it was found that at chance levels of performance in a modified T-box with visual cues, separate computed averages of hippocampal impedance during correct and incorrect responses showed only irregular deviations around the baseline. At intermediate performance levels, a deep transient fall of 2.0 to 6.0 per cent of the baseline value immediately followed presentation of the test situation, and persisted beyond completion of the task. It was followed by a slow rise, exceeding 8.0 per cent of baseline in some cases, with slow return to the preapproach level after 6 to 8 seconds. This "evoked" response persisted undiminished with considerable overtraining (Fig. 6). Extinction of the learned habit abolished these responses, which reappeared with retraining. No baseline impedance shifts were seen in these hippocampal impedance records during acquisition or extinction of the discrimination.

It has been suggested by Jasper (1965), that these impedance changes provide a measure of "the simple amount of activity," and are not critically related to any obscure molecular change in learning. If this were the case, it would be necessary to take account of the relative magnitude of impedance shifts in situations where the relative amounts of neuronal activity can be specified with reasonable reliability. Such situations are few, but it may be noted parenthetically that the magnitude of the impedance change accompanying a learned response (approximately 15 per cent of baseline peak-to-peak) is of the same order as that seen in spreading depression, associated with a massive depolarization of all neuronal elements in the population, and possibly involving neuroglial elements in a similar process (Weiss, Kado and Adey, 1964). Yet the neuronal duty cycle, and thus the proportion of time per neuron spent in a depolarized state, is substantially less in the learned response than in spreading depression.

More direct evidence of the qualitative, as well as quantitative, relationship of impedance changes to the conditional response has come from a study of impedance shifts in amygdala, hippocampus and midbrain reticular formation. Computed averages have been made of impedance records from these three structures for five days' training, each involving thirty trials in a paradigm with consecutive presentation of an alerting stimulus, then orientation to the test situation, followed by a discriminative performance. These computed averages were made at chance performance level, at criterion, immediately following cue reversal, and in the course of retraining (McIlwain, Kado and Adey, in preparation). Computer analysis covered an 8 second epoch, with approximately 1.5 seconds between presentation of the three successive stimuli. In all three structures, there was a progressive decrease in variance in baseline impedance in the course of training to a high performance level. Immediately after cue reversal, variance throughout the epoch again increased sharply, but declined with retraining in the new paradigm. Impedance responses during a learned response were larger and more consistent in the hippocampus than in the midbrain reticular formation (Fig. 7). Orienting behavior was associated with larger impedance responses in midbrain reticular formation than in the hippocampus. No consistent impedance responses were detected in the amygdala during orienting or discriminative behavior. Reversal of behavioral cues at first exaggerated hippocampal impedance responses, which declined on subsequent training days, but reappeared on reattainment of high performance levels.

5. <u>A consideration of the nature of cerebral impedance responses</u>.

The foregoing account has indicated qualitative and quantitative aspects of impedance changes that are both regionally determined and critically dependent on levels of training. They certainly do not appear to relate simply to the amount of activity in the particular tissue, and even if it be argued that they relate to ionic shifts within cerebral compartments (Jasper, 1965), it is obviously necessary that we seek an understanding of underlying mechanisms, which may involve macromolecular systems. We have previously discussed impedance current flow in a tricompartmental model, with neuronal, neuroglial and extracellular compartments (Adey, Kado, Didio and Schindler, 1963). The neuroglial compartment, essentially enclosing the neurons in many areas, may be regarded as intervening between the neuron and the blood vascular system in metabolic exchanges, and as forming a micrometabolic module of neuronal and neuroglial elements (Barrnett, 1963; Hydén and Egyhazi, 1962). Preferred current pathways would lie in low resistance shunt paths in the extracellular space and in neuroglia, rather than through neurons. These impedance responses may occur in non-neuronal compartments, including neuroglia.

The evidence suggests that impedance responses reflect changes in intrinsic characteristics of cerebral tissue, rather than relating directly to such factors as cerebral blood flow or blood pressure (Adey, Kado and Walter, 1965). These changes may relate more closely to tissue carbon dioxide levels than to vascular factors. Carbon dioxide metabolically produced may undergo conversion to carbonic acid in the presence of carbonic anhydrase. This reaction may occur within the neuroglial compartment. Obviously, these ionic shifts may be controlled by other more complex factors, and the notion that carbon dioxide may be the ultimate arbiter should be treated cautiously.

More explicit evidence on the role of the neuronal content of cerebral tissue in these evoked impedance responses has been gleaned from studies in the cat (MacGillivray, Kado and Adey, 1965). Ethyl alcohol at blood levels up to 240 mg/100 ml produced lowered resistance and increased capacitance in amygdala, hippocampus and lateral geniculate body of the cat. Following retrograde degeneration of about 80 per cent of the neuronal population in the lateral geniculate body, alcohol no longer produced the characteristic response in the degenerated tissue (Fig. 8). Similar differential responsiveness between normal and degenerated geniculate tissue occurred with a psychotomimetic cyclohexamine drug. The evidence thus suggests that a normal neuronal population is essential to the impedance responses. Since the relatively high impedance of neuronal elements makes it unlikely that they are the site of changed conductance discernible in measurements across the tissue as a whole, the question thus arises as to whether neurons may exercise a controlling influence on conductance characteristics in their environment, involving extracellular fluid and neuroglial envelopes.

While it would be easy to dismiss the extracellular compartment as a mere bucket of saline, if our notions of cerebral organization required it merely to contribute sodium or other cations, attention has recently been focused on its content of mucopolysaccharide material, which may exhibit considerable organization in the arrangement of these large molecules. They are capable of modulating and controlling rates of ionic movements through this compartment. They have been shown to be chemically disarranged in the types and location of their sugar molecules in mental disorders (Barker, Bayyuk and Stacey, 1962). Their presence in ground substance of brain tissue has long been recognized, but their functional significance, and that of the extracellular compartment generally, has received little attention.

6. <u>Hippocampal organization as a model of cerebral processes in attention and learning</u>.

We may conclude that hippocampal participation in learning involves establishment of functional patterns with subcortical structures, and thus, with diencephalocortical paths involved in sensory systems. The degree of these interrelations appears to change subtly and swiftly from moment to moment. Assessed on the basis of simultaneous EEG records from hippocampal and extrahippocampal structures, analyzed with such techniques as are currently available for detection of linearly shared spectral components, we have glimpsed some of the plastic and complex patterns characterizing alerting, orienting and discriminative behavior (Adey and Walter, 1963; Radulovački and Adey, 1965; Walter and Adey, 1963; Walter, 1963; Walter and Adey, 1965 a and b). Within the hippocampus, at least, patterns of theta activity established in the course of training exhibit increasing regularity, and their reestablishment with each behavioral performance has a degree of probabilistic scatter suggesting their organization on a "best fit" basis. Do these wave patterns, then, underlie the initial deposition of information in cerebral tissue, and is its subsequent recall dependent on the reestablishment of a pattern of waves to which the neuron had been previously exposed? The effectiveness of these subsequent wave patterns in eliciting neuronal firing might depend on their multivariate relationship to an "optimal" wave pattern, capable of inducing firing of that neuron at its lowest threshold.

Evidence that these wave processes recorded grossly reflect an intracellular wave phenomenon having similar frequency characteristics has been found by Fujita and Sato (1964) in hippocampal theta trains, and in neocortical neurons by Creutzfeldt, Fuster, Lux and Nacimiento (1964) and by Elul (1964). Elul has noted that, despite similar spectra in the EEG recorded grossly and the intracellular waves, their mathematical coherence is low. This has suggested that the surface EEG may arise in a population of intraneuronal generators as the normal distribution ensuing from their combined activity in a non-linearly related fashion, in accordance with the central limit theorem of statistics (Cramer, 1962). In such a scheme, it would be anticipated that the frequency characteristics of individual generators would relate strongly to the gross EEG, but that phase relations would be lost in the process of summation. The notion that theta wave patterns are indicative of hippocampal inhibition is difficult to support from the concomitant unit firing noted by Fujita and Sato (1964), and the evidence for EPSP activity, rather than IPSP, in the course of theta waves.

At least through the window of a microelectrode within the body of the cortical neuron, firing to produce a propagated spike is not a regular concomitant of the depolarizing phase of the intracellular waves, even where this exceeds the threshold level for firing in some cases (Adey and Elul, 1965). The intracellular wave and initiation of a propagated impulse thus appear to involve processes that may occur in parallel in individual neurons, and may bear non-linear interrelations to one another.

We have thus come to recognize the critical difference between the sensing of physiological processes that relate to transmission and transaction of information, as opposed to its storage. These studies have emphasized the peculiar nature of cerebral cellular organization, epitomized in many aspects by the hippocampus; a dendritic tree substantially larger than the volume of the cell body, overlapping and perhaps physically contiguous with those of neighboring neurons; a neuroglial compartment intimately involved in neural metabolic exchanges; and an extracellular compartment disposed between neuronal and neuroglial elements and characterized by a substantial content of macromolecules.

Acknowledgments

These studies were supported by Grants NB-01883 and MH-03708 from the National Institutes of Health, by Contract AF 49(638-1387) from the U. S. Air Force Office of Scientific Research, by Contract NONR 233(91) from the Office of Naval Research, and by Contract NASA NsG 502 from the National Aeronautics and Space Administration.

References

Adey, W. R. 1961. Brain mechanisms and the learning process. C. Judson Herrick Memorial Symposium, Chicago, 1960. Federation Proc. 20: 617-627.

Adey, W. R. 1965. Electrophysiological patterns and cerebral impedance characteristics in orienting and discriminative behavior. Symposium on "Neural Mechanism of Conditioned Reflex and Behavior." Proceedings of International Union of Physiological Sciences. XXIII International Congress, Tokyo, 1965, 4: 324-329.

Adey, W. R., F. R. Bell and B. Dennis. 1962. Effects of LSD-25, psilocybin, and psilocin on temporal lobe EEG patterns and learned behavior in the cat. Neurology 12: 591-602.

Adey, W. R. and C. W. Dunlop. 1960. The action of certain cyclohexamines on hippocampal system during approach performance in the cat. J. Pharmacol. exper. Therap. 130: 418-426.

Adey, W. R., C. W. Dunlop, and C. E. Hendrix. 1960. Hippocampal slow waves; distribution and phase relations in the course of approach learning. A.M.A. Arch. Neurol. 3: 74-90.

Adey, W. R. and R. Elul. 1965. Nonlinear relationship of spike and waves in cortical neurons. Proc. American Physiological Society, Los Angeles, September, 1965. The Physiologist 8: 98.

Adey, W. R., R. T. Kado and J. Didio. 1962. Impedance measurements in the brain tissue of chronic animals using microvolt signals. Exper. Neurol. 5: 47-66.

Adey, W. R., R. T. Kado, J. Didio and W. J. Schindler. 1963. Impedance changes in cerebral tissue accompanying a learned discriminative performance in the cat. Exper. Neurol. 7: 282-293.

Adey, W. R., R. T. Kado and D. O. Walter. 1965. Impedance characteristics of cortical and subcortical structures; evaluation of regional specificity in hypercapnea and hypothermia. Exper. Neurol. 11: 190-216.

Adey, W. R., R. Porter, D. O. Walter and T. S. Brown. 1964. Prolonged effects of LSD on EEG records during discriminative performance in cat; evaluation by computer analysis. Electroenceph. clin. Neurophysiol. 18: 25-35.

Adey, W. R. and D. O. Walter. 1963. Application of phase detection and averaging techniques in computer analysis of EEG records in the cat. Exper. Neurol. 7: 282-293.

Adey, W. R., D. O. Walter and C. E. Hendrix. 1961. Computer techniques in correlation and spectral analyses of cerebral slow waves during discriminative behavior. Exper. Neurol. 3: 501-524.

Adey, W. R., D. O. Walter and D. F. Lindsley. 1962. Effects of subthalamic lesions on learned behavior and correlated hippocampal and subcortical slow wave activity. A.M.A. Arch. Neurol. 6: 194-207.

Barbizet, J. 1963. Defect of memorizing of hippocampo-mamillary origin: a review. J. Neurol. Neurosurg. Psychiat. 26: 127-135.

Barker, S. A., S. H. I. Bayyuk and M. Stacey. 1962. Chemistry of a case of juvenile amaurotic idiocy. Nature 196: 64-65.

Barrnett, R. J. 1963. Fine structural basis of enzymatic activity in neurons. Trans. Amer. Neurol. Assoc. 88: 123-126.

Bremner, F. 1964. Hippocampal activity during avoidance behavior in the rat. J. comp. physiol. Psychol. 58: 16-22.

Cramer, H. 1955. "The Elements of Probability Theory." New York, Wiley.

Creutzfeldt, O. D., J. M. Fuster, H. D. Lux and A. Nacimiento. 1964. Experimenteller Nachweis von Beziehungen zwischen EEG-wellen und Activität corticaler Nervenzellen. Naturwissensch. 51: 166-167.

Drachman, D. A. and A. K. Ommaya. 1964. Memory and the hippocampal complex. A.M.A. Arch. Neurol. 10: 411-425.

Elul, R. 1964. Specific site of generation of brain waves. The Physiologist 7: 125.

Fujita, Y. and T. Sato. 1964. Intracellular records from hippocampal pyramidal cells in rabbit during theta rhythm activity. J. Neurophysiol. 27: 1011-1025.

Grastyan, E. 1959. The hippocampus and higher nervous activity. In "The Central Nervous System and Behavior," Transactions of the Second Conference (M. A. B. Brazier, ed.), pp. 119-193. New York, Josiah Macy Jr. Foundation.

Grastyan, E., K. Lissak, I. Madarasz and H. Donhoffer. 1959. Hippocampal electrical activity during the development of conditioned reflexes. Electroenceph. clin. Neurophysiol. 11: 409-430.

Green, J. D. and A. A. Arduini. 1954. Hippocampal electrical activity in arousal. J. Neurophysiol. 17: 532-557.

Hydén, H. and E. Egyhazi. 1962. Nuclear RNA changes of nerve cells during a learning experiment in rats. Proc. Nat. Acad. Sci., Washington 48: 1366-1373.

Jasper, H. H. 1965. In "The Analysis of Central Nervous System and Cardiovascular Data Using Computer Methods," National Aeronautics and Space Administration, Washington (eds. L. D. Proctor and W. R. Adey). NASA Document SP-72, p. 138.

Jung, R. and A. E. Kornmüller. 1938. Eine Methodik der Ableitung lokalisierter Potentialschwankungen aus subcorticalen Hirngebieten. Arch. Psychiat. Nervenkr. 109: 1-30.

Kamikawa, K., J. T. McIlwain and W. R. Adey. 1964. Response patterns of thalamic neurons during classical conditioning. Electroenceph. clin. Neurophysiol. 17: 485-496.

MacGillivray, B., R. T. Kado and W. R. Adey. 1965. The effects of alcohol on brain tissue impedance in animals and man. In press.

Monroe, R. R. and R. G. Heath. 1961. Effects of lysergic acid and various derivatives on depth and cortical electrograms. J. Neuropsychiat. 3: 75-82.

Porter, R., W. R. Adey and T. S. Brown. 1964. Effects of small hippocampal lesions on locally recorded potentials and on behavior performance in the cat. Exper. Neurol. 10: 216-235.

Pribram, K. and M. Mishkin. 1955. Simultaneous and successive visual discrimination by monkeys with inferotemporal lesions. J. comp. physiol. Psychol. 48: 198-202.

Radulovački, M. and W. R. Adey. 1965. The hippocampus and the orienting reflex. Exper. Neurol. 12: 68-83.

Sokolov, E. N. 1963. Higher nervous functions: the orienting reflex. Ann. Rev. Physiol. 25: 545-580.

Vinagradova, O. S. 1961. "Orientirovochnyi Reflex i ego Neyrofiziologicheskic Mechanizmi." Izd-vo APN RSFSR, Moskva.

Walter, D. O. 1963. Spectral analysis for electroencephalograms: mathematical determination of neurophysiological relationships from records of limited duration. Exper. Neurol. 8: 155-181.

Walter, D. O. and W. R. Adey. 1963. Spectral analysis of electroencephalograms during learning in the cat, before and after subthalamic lesions. Exper. Neurol. 7: 481-503.

Walter, D. O. and W. R. Adey. 1965a. Analysis of brain-wave generators as multiple statistical time series. Inst. Electrical and Electronic Engineers, Trans. Biomed. Eng. 12: 8-13.

Walter, D. O. and W. R. Adey. 1965b. Linear and nonlinear analysis of intracerebral relationships by stochastic modeling. Ann. New York Acad. Sci. In press.

Weiss, T., R. T. Kado and W. R. Adey. 1964. The reactive component of impedance during spreading depression and anoxia in relation to ohmic resistance, DC potential, EEG and surface temperature in the cortex. The Physiologist 7: 283.

Legends to Figures

Fig. 1. Typical EEG tracings in control records (A) and on days after a psychotomimetic cyclohexamine (B) during T-maze discriminative responses (left) and orienting responses (right). Vertical bar line indicates moment of behavioral presentation, including onset of 500 cycles per second tone. After drug, regularity of 6 cycles per second activity was enhanced during discrimination, and in orienting responses, slower wave trains were also enhanced. Note leads exhibiting much fast activity during intertrial epochs (trial 24, 5-6, 12-13) which changed to 6 cycles per second "theta" activity during discrimination, and a 4 to 5 cycles per second train during orientation (see text). (From Radulovački and Adey, 1965).

Fig. 2. Bipolar EEG records from a series of closely spaced leads in right and left dorsal hippocampi during performance of the discriminative task on six different days, showing changes produced by electrolytic lesions at LDH 2, 3 and 4 and at RDH 5 and 6. (From Porter, Adey and Brown, 1964).

Fig. 3. Comparison of computed averages of 40 daily trials from a bipolar channel adjacent to electrolytic lesion on nine consecutive days before and after production of small regions of damage in both hippocampi, showing transient increase in synchrony. For both series, behavioral performance remained between 85 and 100 per cent correct. (From Porter, Adey and Brown, 1964).

Fig. 4. Computed averages of epochs of left and right hippocampal EEG records during approach performance on days before LSD (A), the day of LSD dosage (B), and days after LSD (C). There was an increase in the

amplitude and regularity of the averages following LSD. This maximized 3 days after the drug (C, 2/1/63), and declined thereafter. (From Adey, Porter, Walter and Brown, 1965).

Fig. 5. Effects of a single dose of LSD on hippocampal EEG, with typical augmentation of discriminative averages from third to tenth day after drug (A). In similar averages of orienting responses (B), a more regular average appeared about the tenth day (3/14/64), and persisted for approximately 10 days, but was consistently slower than averages during discrimination (see text). (From Radulovački and Adey, 1965).

Fig. 6. Development of regularity in EEG wave trains and appearance of impedance responses in hippocampus during acquisition of visual discriminative performance in modified T-maze. Computed averages of EEG records (A) at chance levels of performance were essentially irregular; showed some regularity at 80 per cent correct; and sustained regularity at 100 per cent. Impedance records at the same levels of training (B) initially showed only irregular perturbations; at 80 per cent a small fall at the start of the performance followed by a rise; and at 100 per cent a profound fall, outlasting the performance. In its full configuration (C), the response is biphasic and lasts about 5 seconds. Approach to food lasts about 1.5 seconds.

Fig. 7. Impedance measurements at 1000 cycles per second, made in approximately 1.0 cmm of hippocampal tissue, when the cat was fully trained (A), immediately after cue reversal (B), and in the course of retraining after cue reversal (C). Each graph shows 3 traces, the mean

and upper and lower limits of variance. Each average was prepared from 5 days' training, with 30 trials daily. Vertical bars indicate successive presentations of tone, visual cues and opportunity to approach food. There was a marked increase in variance throughout analysis epoch following cue reversal. Variance decreased with retraining (B). "Evoked" impedance response during discrimination, amounting to about 10 per cent of baseline impedance at 100 per cent performance, waned following cue reversal, but was reestablished with retraining (C). At 100 per cent performance (A) variance in capacitive lead declined progressively from moment tone was presented to commencement of approach and remained narrow throughout remainder of analysis. No comparable "evoked" responses during discrimination were seen in similar analyses from midbrain reticular formation or amygdala (see text). (From McIlwain, Kado and Adey, in preparation).

Fig. 8. Resistive and capacitive changes in the degenerated (right) and normal (left) lateral geniculate body in the cat following infusion of ethyl alcohol. Blood alcohol 30 minutes after infusion was 230 mg/100 ml. Note the absence of response on the ablated side. Solid line, effects of alcohol; dashed line, control injection of Ringer lactate solution used as vehicle for alcohol. Infusion began at vertical line. Abbreviations: A.L.G., coaxial electrode in anterior region of lateral geniculate nucleus; P.L.G., coaxial electrode in posterior (cellular) region of lateral geniculate. (From MacGillivray, Kado and Adey, 1965).